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Developing and Pilot Testing an fMRI Paradigm to Assess Negative Emotional Effects in 2nd Graders with Developmental Dyscalculia

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1 Abstract

Developmental Dyscalculia (DD) is a specific math learning disability that has been shown to persistently impair numerical and arithmetical development in affected individuals. The underlying neurological mechanisms are still debated and their relation to negative emotional processing stays elusive. The aim of this study was to investigate in the interaction between mathematical performance and negative emotions in DD and to assess its neural activation correlates. To approach this question, we developed and piloted a novel block-based functional magnetic resonance imaging (fMRI) paradigm. With it, we behaviorally tested subtraction problem solving and a novel control task during stress and non-stress conditions in 13 children and 10 adults without math learning deficits. Furthermore, the brain activity in the adults was in parallel assessed by fMRI scanning. Against our hypotheses, we found no centralized parietal activation during the math task but rather the involvement of regions related to basal numerical processing. Our results further revealed a positive stress effect on subtraction problem solving during stress condition. In addition, activation in brain areas associated with stress and anxiety was increased. These findings empathize the further testing of the paradigm in individuals with DD which could help to disentangle the interplay between negative emotional processing and math disabilities.

2 Introduction

2.1 Developmental Dyscalculia – A Specific Developmental Learning Disability

Developmental Dyscalculia (DD) is a specific learning disability that is characterized by an impaired development of basic arithmetical competencies. The individual's abilities to acquire numerical concepts and procedures are significantly lower than can be explained by age, schooling, and level of intelligence. With an estimated prevalence ratio between 3 and 6% the disorder is a fairly common learning disorder (Kucian, 2016; Shalev and Aster, 2008). The relative abundancy in each gender was debated as previous studies showed both, higher ratio of girls (Fischbach et al., 2013) and of boys (Reigosa-Crespo et al., 2012) being affected. A recent study in large children found that girls were more prone to develop math learning disabilities especially with more pronounced DD (Schulz et al., 2018). Independent of gender, the first signs of diminished arithmetical functioning typically emerge in primary school age when children face mathematics the first time. However already in preschoolers, age specific precursor skills can predict the later establishing numerical skills and are thereby potential DD indicators (Stock et al., 2010). Although DD is attributed to genetic and environmental factors, the hereditary component seems to be only of modest causation (Kucian and Aster, 2014).

The disorder presents itself in a heterogenous manner. A wide range of individual impairments might occur in various aspects of numerical and arithmetic functioning, including also non-numerical competencies. Thereby, children affected with DD frequently have difficulties with counting skills, magnitude processing, arithmetic, transcoding of number words, digits and quantities, or the spatial number representation. Furthermore, domain general skills like working memory, attention, or executive function might be affected (Kucian and Aster, 2014). Impairments in these more domain general characteristics are also typically observed symptoms in other neurocognitive disorders like dyslexia and attentional deficits (ADHD). Both are frequently described comorbidities and might have commonalities in their etiology. Pure DD on the other hand seems to be rather the exception (Kuhn, 2015).

2.1.1 Brain Imaging in Developmental Dyscalculia

Structural magnetic resonance imaging (MRI) of DD patients showed an atypical brain structures of frontal and parietal regions. Especially grey matter volume in the right intraparietal sulcus (IPS) was found to be reduced (Price and Ansari, 2013; Rotzer et al., 2008). The IPS is suggested to be the core area for the processing of number magnitude, even if no numbers are involved (Butterworth and Walsh, 2011). Thereby, structural analyses have been indicating this region and parietal regions in general to play a key role in DD.

These findings have been further corroborated by functional magnetic resonance imaging (fMRI). For instance weaker activation in the left IPS (Kucian et al., 2006) but also reduced bilateral IPS and general decreased parietal activity (Ashkenazi et al., 2012; Kucian et al., 2011) was found in children with DD. However, opposite results have been described as the activity was shown to be increased in the same brain regions (Davis et al., 2009; Rosenberg-Lee et al., 2015). Connectivity analyses further demonstrated both, hypoconnectivity in the superior longitudinal fasciculus (Kucian and Ashkenazi, 2014) but also hyperconnectivity between the IPS and the bilateral frontoparietal network (Michels et al., 2018; Rosenberg-Lee et al., 2015). Although studies have found contradicting results depending onthe activity and functional connection, the regions in close vicinity of the IPS seem to be decisive for the emergence of dyscalculia. The differences might result from the task varieties, the fMRI parameters or different DD inclusion criteria (Kucian, 2016). It has been proposed that children with DD might undergo a delayed development of the areas crucial for numerical processing. Where regions associated for numerical cognition will normally undergo an anterior-posterior shift during childhood, DD could be caused by a reduced maturing of parietal regions. Thereby, they might be forced to use more frontal regions as compensatory strategies and would therefore lack the more centralized, automated, and more efficient numerical processing (Kucian and Aster, 2014; McCaskey et al., 2018). Nevertheless, many domain-general brain regions seem to be involved in the disorder, next to parietal areas this includes also frontal areas, attributed to executive functions and working memory, and also occipital, temporal, and subcortical regions (Bulthé et al., 2019). Further research is needed to fully disentangle the mechanisms underlying math disabilities.

2.1.2 Diagnosis of Developmental Dyscalculia

Together with the high occurrence of comorbidities the neural underpinnings of DD suggest that multiple cognitive deficiencies rather than a single core deficit are causing the disorder. Summarized, this diversity in neurocognitive functions of DD gives each individual a unique set of strengths and weaknesses in these numerical and non-numerical competencies. Therefore, to diagnose DD arithmetic processes and domain-general abilities should be assessed multidimensionally (Kucian, 2016). Former guidelines for the diagnosis of DD included the necessity of a discrepancy between arithmetical and general achievement. However, this was of debate as the latter is commonly measured by intelligence (IQ) testing which is conflictingly partially based on numerical skills (Ehlert et al., 2012). The current version of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM, 5th revision) (American Psychiatric Association, 2013) removed this requirement from their diagnosis criteria and set the focus more on profiling individual cognitive abilities based on neuropsychological testing. This seems to be more in line with the contemporary view of the disability.
Currently, brain-based diagnostic of DD is not yet on the level of standardized neuropsychological assessments. However, it might be of potential diagnostic value in the near future (Dinkel et al., 2013).

2.1.3 Implications and Interventions

DD is an enduring learning disorder that persists into adulthood (Shalev et al., 2005). Thereby it might have a big impact on the individual's scholastic achievement and later employment possibilities leading to vast public costs. Additionally, secondary symptoms like anxiety and depression can develop affecting the emotional wellbeing and further increase the economic burden (Gross et al., 2008; Parsons and Bynner, 2005). This emphasizes the importance of the research in the field of numerical learning deficits.
Only few studies investigated DD treatments and their long-term benefits. For instance, it could be shown that with direct one-on-one tutoring for eight weeks of children with mathematical learning disabilities the performance in counting strategies and the retrieval of arithmetic facts could be improved. Furthermore, the brain activity patterns adjusted to those of the control children (Iuculano et al., 2015). Additionally, five-week computer based mental number line training improved spatial number representation and arithmetic problems solving in children with and without DD. Functional imaging was further able to show a modulation of their brain functions by activating less supporting regions of the frontal lobe (executive functions) but increased activation in the IPS (Kucian et al., 2011). Five-week training with an extended version of this computer program lead to the disappearance of a previously examined functional hyperconnectivity in children with DD (Michels et al., 2018). Another computer based spatial cognitive training could recently show a mathematical learning improvement in a large children cohort study. However, results concerning specifically math learning deficits are still pending (Judd and Klingberg, 2021).
Summarized, interventions like learning therapies and supporting computer applications have shown to be able to ameliorate numerical skills and change brain activity and connection in children with DD. Further long-term investigations based on current neuropsychological knowledge and brain imaging findings are still needed. Nevertheless, the focus should always lie on setting individual treatment goals and on optimizing the general learning environment (Kucian and Aster, 2014).

2.2 Math Anxiety

Negative emotion against mathematics are commonly observed in children and in some cases even develop to a severe form of math anxiety (MA). With prevalence estimates going up to 30%, MA is rather common, and the number seems to be increasing with age. Thereby women showed to be more frequently affected but with the tendency to be equally distributed on both genders at children age (Dowker et al., 2016). MA can be attributed to both genetic predisposition, but also environmental factors like schooling and parental math relationships (Maloney et al., 2015; Wang et al., 2014).

MA is a specific anxiety towards math and can be separated from general test anxiety (Kazelskis et al., 2000) and state anxiety (Hembree, 1990). It is described as feelings of tension towards manipulating numbers and the solving of arithmetic problems (Richardson and Suinn, 1972). Immediate math avoidance behavior in math anxious individuals can already be observed in the early attentional processing of mathematical information when engaging in a task (Hopko et al., 2002; Pizzie and Kraemer, 2017). On a physiological level, symptoms like increased heart rate, sweating, stomach ache can emerge (Blazer, 2011). In addition, increased cortisol levels were associated with decreased math achievement in high math anxious (HMA) individuals. Low math anxious (LMA) controls on the other hand performed better with if their cortisol levels were increased (Mattarella-Micke et al., 2011). In general, individuals with MA tend to solve mathematical task worse than LMA peers. This results in a reciprocal relationship between mathematical achievement and MA. Thereby, it has detrimental long-term consequences with affected individuals tending to have reduced employment prospects (Dowker et al., 2016).

Especially children with mathematical learning disabilities have shown to display higher levels of MA than their achieving peers (Kucian et al., 2018a; Wu et al., 2014). This is in line with the observation that children with DD often develop additional internalizing problems (Graefen et al., 2015). These findings are worrying and emphasize further investigations of the interaction between negative emotions and low math performance on and the interplay between MA and Dyscalculia on neurocognitive level.

Functional Brain imaging of children with MA showed right amygdala hyperactivity during arithmetic task solving. The amygdala has been demonstrated to play a crucial role in the processing of negative emotions (Young et al., 2012). Similar results were replicated by another study that was even able to decrease the amygdala hyperactivity and successfully reduce math anxiety through cognitive tutoring in HMA children (Supekar et al., 2015). Furthermore, structural imaging found associations between higher levels of MA and smaller right amygdala volumes. The authors argue that hyperactivity could have led to cellular atrophy and thereby to decreased grey matter volume (Kucian et al., 2018a). Additionally, increased functional signal in the bilateral dorsal posterior insula of HMA individuals was observed before engaging in a math task. Therefore, already math anticipation was able to activate areas related to visceral threat and pain detection (Lyons and Beilock, 2012a).

For the neuropsychological impact of MA on task solving, it has been hypothesized that the processing of negative emotion demands working memory leading to an affective drop in math performance. Less working memory (WM) remains for the task processing (Ashcraft and Moore, 2009). Furthermore, functional imaging of HMA showed weaker deactivation of the default mode network (DMN) during arithmetic task solving. The DNM is associated with emotional processing and might thereby consume WM resources (Pletzer et al., 2015). This is in line with the findings that performance in HMA individuals was particularly limited for math problems with high WM demands (Ashcraft and Krause, 2007). Another study on children with MA have found reduced activation in areas of the number processing network, including the left IPS and thus claim to have found a direct explanation for reduced numeracy (Young et al., 2012). However, other studies failed to replicate this results (Lyons and Beilock, 2012b; Pletzer et al., 2015). Further behavioral and electro-related potential investigations provide evidence that already basic number processing is impaired in MA individuals (Artemenko et al., 2015). Thus, there is evidence that MA could also directly interfere with numeracy.

Summarized, MA is a specific phobia that has strong psychological and physiological impacts on affected individuals, assumably also through triggering brain networks related to the processing of negative emotions. Furthermore, it impairs math performance leading to scholastic and employment limitations. MA compromises numeracy most likely indirectly by reducing the WM capacity, but might also directly interfere with elementary numerical processing. Its research in relation to math disabilities is of particular interest as they have shown to be more prone to develop it.

2.3 Functional Magnetic Resonance Imaging of the Brain

Functional Magnetic Resonance Imaging (fMRI) is a variant of conventional Magnetic Resonance Imaging (MRI) and provides a reliable and robust tool to study brain activity and connectivity in vivo. It is a non-invasive method that enables whole brain measurement on a high spatial resolution (Soares et al., 2016). Cross-sectional images are acquired using a powerful magnet with strengths ranging between 1.5 to 7 Tesla, three gradients, and radio frequency (RF) coil. In structural MRI, the magnetic field is adjusted on the resonance frequency of hydrogen nuclei, which align themselves with the produced field. Short pulses of radio waves sent by the RF coil disturb the magnetic field and deflect the hydrogen nuclei. After deactivating the radio waves, the nuclei re-align themselves again and reemit electromagnetic waves which are captured by the RF coil (Kashou, 2014). The speed of the hydrogen nuclei and thus the amount of energy released depend on its magnetic environment. Thereby, the tissue composition causes variation in the signal which is then visualized to receive high resolution anatomical 3D brain images that differentiate gray and white brain matter (Yousaf et al., 2018).

Functional brain mapping in contrast uses the blood oxygenation level-dependent (BOLD) contrast technique. It is based on the underlying concept that increased local neural activity requires higher energy consumption, which results in a short-term increased flow of oxygenated blood. The BOLD signal follows a defined pattern also referred to as the hemodynamic response function (HRF). Its shape is dependent on the properties of the local vascular network of the tissue and can be modelled. The canonical HRF is characterized by a gradual increase, peaking at 5 – 6 s, return to baseline after about 12 s and with a small undershoot before stabilizing again after 25 – 30 s (Soares et al., 2016). The change in the ratio of oxygenated (diamagnetic) to deoxygenated (paramagnetic) hemoglobin can be detected by the scanner to create functional 4D brain images. Thus, they include a fourth temporal dimension but are typically lower in spatial resolution than structural 3D scans (Kashou, 2014). In sum, fMRI is a frequently used method to assess and map specific brain activation under various kinds of mental conditions.

The analysis of fMRI data is performed usually in three main stages. (1.) In the preprocessing step the functional 4D images are realigned, potentially corrected for slice-timing and co-registered onto a structural T1 scan of the same subject to correct for movement during the scan. Besides, the images are normalized to a standard stereotactic human brain template and smoothed to increase the signal to noise ratio. (2.) For the first level analysis usually a mass-univariate approach is chosen based on the *General linear Model* (GLM). It performs a statistical test for each voxel individually across all lineages to test how well its signal fits with the predicted model. Latter is calculated by linear convolution of the HRF with the experimental parameters. Additionally, low-frequency noise is eliminated by applying a high pass filter. (3.) In the second level analysis, contrasts are set to statistically compare the activity of the different conditions between the subjects. Thus, it is often referred to as the group level analysis. The results are usually corrected for multiple comparison (James et al., 2014).

2.3.1 Experimental fMRI Design

In the human brain there are constantly spontaneous brain activations even if the person is not engaging in any task and does not receive any external stimuli. This baseline activity can be assessed by resting state fMRI, which can give valuable information about intrinsic signal networks and fluctuations. Nevertheless, fMRI investigations are predominantly task-based with the most frequent used paradigms being event-related, block-based, and mixed designs. *Event-related* designs consists of discrete events of stimuli or tasks that are separated by inter-stimulus intervals (ISI). The ISI are typically random in length (ISI ranging from 0.5 to 20 s) which increase the unpredictability. During *block-designs*, stimuli are presented consecutively as a series of epochs or blocks (typically 15 – 30 s) with the same condition. Thus, the brain activity is cumulated over a short period of time. *Mixed designs* incorporate elements of both event- and block-designs (Soares et al., 2016).
Depending on the design choice and specification, the paradigm can optimize either brain activity detection power, the estimation of the HRF shape, or focus on the conditional randomness of a design. The optimal balance thereby depends on the individual goal of the design (Liu and Frank, 2004). Event-related designs are advantageous for HRF estimation, but they are less efficient to detect brain activity. Block designs on the other hand enable the best power for brain activity detection. However, they contain less elements of randomness and thus might be more predictable for the participant (Henson, 2011). Brain activity can then be assessed by subtracting the activity during task condition from rest or by comparing two or more kinds of tasks with each other.
Independent of paradigm choice, there are certain guidelines to increase design efficiency. For instance, participants should always be kept as busy as possible to maximize the time spent on task. However, breaks of rest should be included as well to allow the HRF to resolve to baseline again. Commonly, a fixation star or cross is presented during the breaks to keep the subject's focus. For block-designed paradigms, it is recommended to use short blocks (18 – 20 s) to increase the statistical power. The reason for that being that consistent use of the same brain area leads to a decrease in signal over time. Furthermore, long blocks are more susceptible to low frequency noise which we later eliminate via high-pass filtering (optimal cutoff: 1/128s ~ 0.01 HZ). For the same reason, trials remote in time should not be contrasted in the analysis (Henson, 2011). To increase the subject's total task time further, the same fMRI run can be performed several times. But one must take possible intra-run variability into account that may occur in terms of measurement deviations and changes in the subject's state (Desmond and Glover, 2002). Lastly for trails that are close together in time, the ISI should be avoided to be a multiple integer of the interscan interval (TR). By including a jitter, the sampling of the HRF is not locked with the stimulus onset, which improves the deconvolution of the HRF (Henson, 2011; Price et al., 2013).

2.3.2 Stress Inducing fMRI Paradigms

The investigation of the effects of math anxiety on brain activity patterns has been in the focus of fMRI research. However, most of the studies classified individuals into HMA and LMA individuals. Their brain activity was then assessed during various kinds of numerical and arithmetical testing and compared between the groups (e.g., Chang et al., 2017; Lyons and Beilock, 2012b; Pizzie et al., 2020; Pletzer et al., 2015; Young et al., 2012). Only a minority of studies tried to elucidate the effects of directly applied stress on math solving behavior and its impact on brain functioning in normal achieving and math impaired individuals. In the following part, the most promising strategies to induce negative emotional load within an fMRI paradigm will be discussed.

Presenting a prime before a task can induce negative emotional effects and influence the individuals solving behavior. Rubinsten and Tannock (2010) found a negative math priming effect on the reaction time in children with DD. By presenting math related words or a word with negative emotional valence before an arithmetic task, the mean reaction time was decreased. They argued that the congruency of the negative priming and the following negative associated math task lead like in a Stroop task to a faster response in children. However, another study failed to demonstrate the same effect by replicating the experiment but presenting their prime words aurally (Kucian et al., 2018b). In addition to words, affective pictures can be used to trigger an emotional response before engaging a task (Bradley and Lang, 2017). Thereby, the effects of math related pictures (e.g., pictures of a classroom, a math test, or a calculator) presented before numerical tasks could be assessed. But no studies could be found implementing these concepts so far.

A very frequently used strategy to increase the affective meaning of fMRI tasks is feedback. Through implementing true and false notifications, the subject retrieves an immediate response of the correctness of the previously solved task. The feedback can be “fair”, where correctly solved tasks lead always to true notifications and incorrect tasks to false ones. This might be the intuitive choice at glance but has the disadvantage that the amount of collected negative and positive responses during the paradigm varies between subjects. Thereby, low math achieving subjects would most likely receive more negative feedback than controls in an arithmetic fMRI task (For examples see: Denervaud et al., 2020 and Feng et al., 2012). On the other hand, also “unfair” feedback can be given by providing false notifications even if the answer would have been correct. Through that, participants might be able to be stressed even more but with the risk of causing confusion and doubtful thoughts (e.g., Allendorfer et al., 2014).

The *Montreal Imaging Stress Task* (MIST) (Dedovic et al., 2005) is a frequently used “unfair” stress task also involving math. During the stress conditions, arithmetic tasks are solved and mostly negative feedback is provided. The subject is further told that his or her performance is below the limit of other contestants. Additionally, the MIST takes advantage of another stressor: time constraints. A decreasing time bar is displayed below the task (Noack et al., 2019).

One other often used stress task is the *Trier Social Stress Test* (TSST) (Kirschbaum et al., 1993), which was deliberately designed to induce stress in adults. The participant must solve arithmetical problems in the scanner while seeing two judges on the screen sitting in front of the camera giving feedback. Social-evaluating stress can thereby be induced.

In sum, the use of primes as stressors is controversial as their effects on task solving and brain activity are still unclear. Feedback on the other hand seem to be a reliable tool to induce pressure and can be further adapted by changing its fairness. In any case, additional measures of anxiety like skin conductance, pulse and respiration rate, cortisol levels, and math anxiety questionnaires can be further corroborating measures to assess the negative emotional effects of a paradigm (Noack et al., 2019). Additionally, one should always have in mind that the MRI investigation is intimidating and most likely induces base-line anxiety in participants, especially in children.

2.4 Aim of this Study

This master thesis is part of a bigger collaboration between the Cuban Neurosciences Center and the Center of MR-Research of the University Children’s Hospital Zurich to transnationally investigate numeracy and wellbeing in children with numerical learning disorders. Therefore, early evidence based neurocognitive profiling in children of pre-kindergarten age up to 2nd graders will be conducted. The main objective of this master thesis is to develop and pilot an fMRI paradigm to assess negative emotional effects related to DD in 2nd graders. We want to elucidate the neural activity underlying their arithmetical functioning to clarify the neurofunctional mechanisms resulting to math disabilities. Furthermore, we aim to investigate in their emotional processing und their capability to cope with stress when engaging with mathematics.

We hypothesize individuals with DD to activate more frontal areas and less parietal regions for arithmetic problem computation as potentially resulted from a delayed development. They should exhibit less-centralized computation and therefore activate more brain regions in general during math tasks than their typically achieving peers. The mean reaction time (RT) of children with DD ought to be higher and accuracy (ACC) distinctly lower in arithmetic but age-appropriate during control tasks. Further, we expect their numerical functioning to be susceptible to stress. The processing of an additional negative emotional load should not only be visible in functional imaging but also diminish their solving success. This negative impact is expected to be the highest during math tasks. Normal achieving controls in contrast should be less affected or might even benefit from the applied pressure. The study will be piloted in adults without any form of math learning disability. The task will therefore be quite feasible for them. Nevertheless, we still expect brain areas to be activated that are related to numerical processing. We hypothesize an increased activation in parietal areas, especially the IPS during arithmetic problem solving. In addition, they will reach high ACCs and low RTs on the behavioral measures. Although the stressor might activate stress-related brain areas (e.g., the insula or the amygdala) it assumably will not impair their solving achievement.

3 Methods

3.1 Participants and Procedure

For the piloting of the fMRI task a total of 10 adults were assessed by functional MRI at the Center for MR-Research of the University Children's Hospital Zurich. All the participants received oral and written study information and provided a signed consent. This piloting study was running under an ethic form that was approved by the Ethics committee of Zurich, Switzerland. Furthermore, MRI eligibility was examined through a MR-Safety questionnaire. The participation was reimbursed with a voucher (20 CHF).
Additionally, behavior in 16 children (1^{st} – 3^{rd} grade) from the Primary School Stocken, Wädenswil was analyzed. They solved computer versions of the same fMRI task. We hope by this means to gain further insight into the adequacy of the paradigm for children of the same age as our DD target group.

3.2 fMRI Task

To assess negative emotional effects related to DD we designed a block-designed fMRI task for 2^{nd} graders to solve arithmetic problems while their blood oxygen-level dependent (BOLD) activation is measured by fMRI scanning. Because the same scan protocol is planned to be further used in Cuba, all the provided instructions are language independent using only symbols. The paradigm contains two task types, arithmetic, and control tasks. In addition, stress and non-stress conditions are examined. Thus, we end up with a factorial design of four different block types (**table 1**).

Factorial Design	Main effect of Condition	
Main effect of task	A. Subtraction	B. Subtraction + Stress
	C. Control	D. Control + Stress

Table 1. Factorial paradigm design with two task types (subtraction and control) and two different conditions (stress and no stress). Thereby, four different block types (A, B, C and D) arise.

The subtraction task contains subtraction problems that are adapted from the age-normalized standardized test inventory DIRG (Diagnostisches Inventar zu Rechenfertigkeiten im Grundschulalter) which is designed to assess numeracy in primary school age (1^{st} – 4^{th} grade) (Grube et al., 2010). We chose subtractions because they are less learned by heart and more demanding than additions. Furthermore, they seem to be especially challenging for DD and thereby crucial discriminators for their arithmetical competencies (Rosenberg-Lee et al., 2015). We also chose not to switch between additions and subtractions as we know that DD often have problems with executive functions, which are demanded in task-switching.
Presented in the form of $a - b = c$, the participants decide if the equation is correct or wrong by answering with an fMRI compatible response box. The subtractions are presented in a fixed order. Each arithmetic block starts with two easy small subtractions (where $5 \leq a \leq 10$, $2 \leq b \leq 8$ and $2 \leq c \leq 8$). After that, more demanding tasks follow. Large subtractions without crossing the number 10 boundary (where $12 \leq a \leq 20$, $2 \leq b \leq 9$ and $10 \leq c \leq 18$) and subtractions crossing 10 (where $11 \leq a \leq 18$, $2 \leq b \leq 9$ and $2 \leq c \leq 9$) are presented alternately. The latter subtraction type is expected to be the most demanding for children at this age and show the lowest expected success rate in the DIRG classification. We chose to increase the level of difficulty within the first tasks of each block to ensure a minimum of tasks to be solved even by low-achieving children.
The amount of correct and incorrect math problems is balanced in each block. Incorrect answers deviate by ±1 to avoid solving by estimation (Ashcraft and Battaglia, 1978; Rosenberg-Lee et al., 2015).

Each block starts with a 3000 ms long block cue indicating the subsequent subtraction problems (**figure 1**, **A** and **B**). In addition, true and false symbols are displayed to remind the correspondence of the buttons. After a blank of 1000 ms, the task section starts by successively presenting math problems for 6000 ms during which the participants can respond. If no answer is provided in the given time the task will be labelled as missed. A short break of 750 ms separates the tasks that are solved in a self-paced manner. Thereby, we want to maximize the time spent on task. However, faster participants will solve more subtractions per block than slower participants will. The whole task procedure will last 19 s on average with a possible range of 15.7 to 21.7 s depending on the speed of the participants. Each task is carried out to completion once it has started.

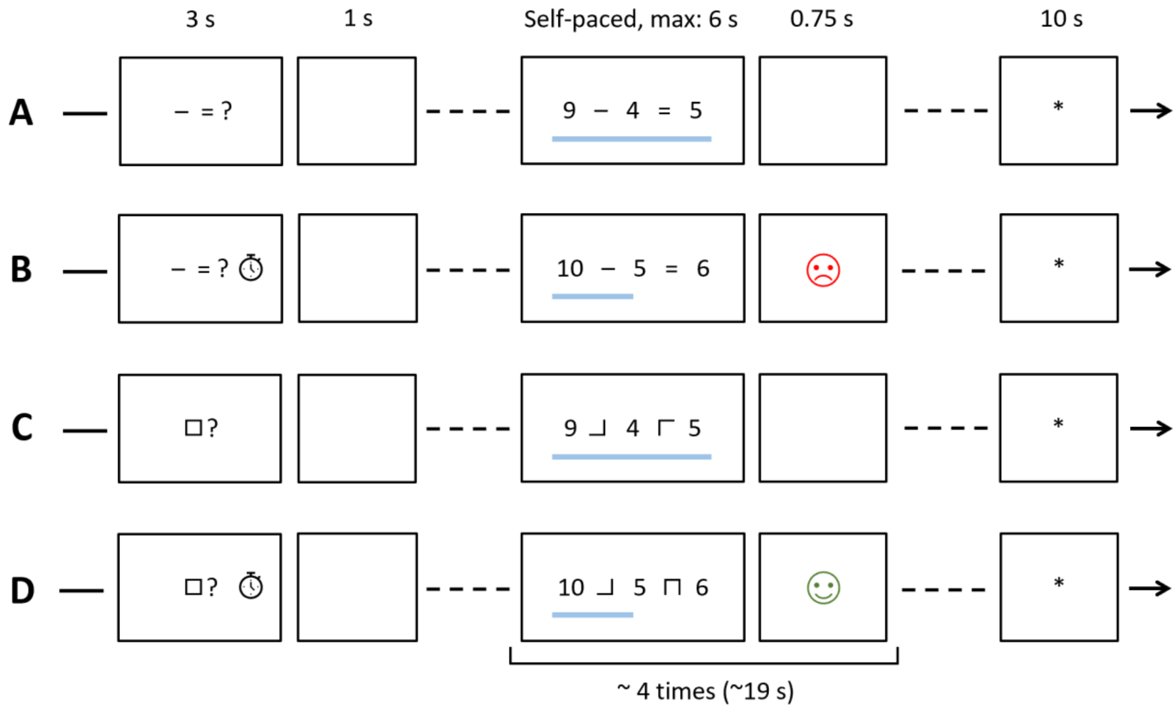

Figure 1. Procedure of the four block types A, B, C and D. All of them start with displaying a block cue (3000 ms), followed by a blank (1000ms). During the subsequent task sequence, tasks are solved self-paced (max. 6000 ms) with a short intertrial interval (750 ms). The blocks last 15.7 – 21.7 s (average: ~19 s) and is followed by a fixation screen (10 s). **A** and **B** contain subtractions that are introduced by a math cue. **C** and **D** compromise square problems initiated with a square cue. The stress conditions **B** and **D** are further cued by a time restriction symbol. The subsequent tasks are then accompanied by a decreasing time bar and additional feedback instead of a blank in the intertrial interval.

The control task must be cognitively demanding without the use of arithmetical processing. We decided against the use of a language related task due to the high comorbidity chance of dyslexia. In addition, the requirement of heavy visuo-spatial memory demands should be avoided as they are often impacted in DD. Therefore, a new control task was designed where participants mentally match two line-shaped objects and judge if they together form a square. The two objects are based on squares where either one, two, or three sides are invisible. During the mental overlapping, the objects are not allowed to be rotated but may overlap. All unclear square-matching problems were excluded. For both tasks to be as visually similar as possible, the same numbers that were used in the math problems are displayed in the control task. However now by the two objects replacing the minus and the equal sign. Equal to the subtraction task composition, we categorized the square problems in terms of their difficulty and increased it during the block. However, the categorization was merely performed non-empirically and further evaluation of the individual task difficulty would be beneficial.
Equivalent to the arithmetic block design, the block starts with a block cue (3000 ms), followed by a blank (1000 ms) and the self-paced control tasks (each max. 6000ms) that are separated by a blank

(750ms) (**figure 1**, **C** and **D**). Each block of tasks is set to last about 19 s with a possible range of 15.7 to 21.7 s. The numbers of tasks solved per block varies due to solving speed differences.

To assess the effects of negative emotional loads on their solving behavior, additional blocks of mild stress were engineered equally for both task types, arithmetic, and control. Thereby, we adapted some of the previously discussed stressors (paragraph 2.3.3) and made them more children compatible. A time bar is placed below the subtraction and the square matching problems. In the stress conditions, the bar gets gradually reduced from right to left in 20 steps of 300 ms. By that, a feeling of time pressure should be stimulated without actually shortening the answer window. In the non-stress conditions, the bar is displayed but not shortened. Before each stress block, a stopwatch symbol was added to the block cue to symbolize the next task will be time restrained. Furthermore, we implemented visual and aural feedback. A green happy smiley together with harmonic sound appear if the correct answer is chosen. False answers and missed responses on the other hand are followed by a red sad smiley combined with dissonant tones. Both smileys are displayed for 750 ms in the inter-task breaks. To balance the visual input as best as possible the smileys are made isoluminant to be of identical perceived brightness. It seemed adequate to give only fair feedback for children to prevent any undesired confusion. However, we expect DD to receive more negative feedback during the paradigm. These chosen stressors are deliberately much milder compared to others from previously discussed stress paradigms. Nevertheless, they should still evoke certain pressure and be of reasonable efficacy for second graders.

Each block is followed by a fixation window where participants are advised to fixate a star (*) in the middle of the screen. Together with the next block cue and the blank a total ISI of 14.75 s should allow the HRF to restore again before the start of the next task. We decided to present all four block types in one paradigm. Thereby, all conditions are close together and it is possible to contrast all of them. However, we end up with less time for each condition and thus reduce our detection power. All four blocks together, plus fixation will last at maximum 144 s, which should be short enough in respective of the high pass filtering. The four block types are presented in a fixed alternating order. One run will take about 395 ± 35 s, due to the block length deviations. In total two runs with unique tasks are performed with a 5 min break in between. Over the course of both runs, the participants will solve 24 blocks and therefore six of each condition. We expect them to solve on average four trials per block, which leaves us with 24 trials for each condition.
Between the participants the block sequence is altered and balanced with the only limitation that the two blocks with the same task type should always be presented successively. Furthermore, the answer buttons and the corresponding symbols for the true and false answers were exchanged for half of the participants. Nevertheless, the corresponding buttons were kept the same during both runs. In total four different paradigm versions were created.
The paradigm was programmed on E-Prime 3.0 [*Psychology Software Tools* (PSTNet), USA]. With its interactive surface, the user can easily design task procedures with inbuilt answer possibilities that appear consecutively on a screen at exact time stamps.

3.3 Behavioral Testing in Children

Computer versions of the same fMRI paradigm were created for the behavioral testing of the primary school students. Equal to the procedure in adults, the participants were instructed, and each solved a practice run before attempting one of the final paradigms. The tests were performed on laptops and the answers were provided by pressing two marked keys. The correspondence of the keys for true and false answers as well as the block order were equally balanced.

3.4 Brain Image Acquisition in Adults

Before each scan, each participant solved a practice run on the computer to explain and get familiar with the fMRI tasks. They were carefully briefed, and MRI safety requirements checked. Around their torso the breathing belt setup was installed to continuously record the respiration. On their right index finger the pulse measurement was attached. After further supplying them with hearing protection, their head was stabilized with padding to minimize head motion. Visual input was provided by MR suitable goggles. Additionally, they received aural input via headphones and answered with an MR compatible response box.
MRI data were acquired on a 3T General Electric Signa Scanner (GE Medical Systems, USA) using an 8-channel head coil. Whole brain functional images were obtained interleaved with a gradient echo EPI sequence [38 slices, slice thickness (ST) = 3.0mm, inter-sliced spacing = 0.3 mm, matrix size (MS) = 64 x 64, field of View (FOV) = 240 x 240 mm, in-plane resolution = 3.75 x 3.75 mm, flip angle (FA)= 74°, echo time (TE) = 32 ms, repetition time (TR) = 1900 ms]. Furthermore, T1-weighted anatomical images were acquired with a fast-spoiled gradient echo sequence (3D FSPGR, ST = 1 mm, no interslice skip, MS = 256 x 192, FOV = 256 x 200 mm, in-plane resolution = 1.00 x 0.96 mm, TE = 5 , FA = 8°, TR = 11).

3.5 Data Analysis

3.5.1 fMRI Preprocessing

MRI data were processed using Statistical Parametric Mapping (SPM12, The Wellcome Trust Center for Human Neuroimaging, UK) running under MATLAB (Release 2012b, The MathWorks Inc., USA). The subject's functional scans were realigned and un-warped. Besides, the images were slice-time corrected in respective to the interleaved and ascending image acquisition. The mean functional image from the realignment was used as a reference scan and was co-registered to the subject's T1-weighted anatomical template. Subsequently, the anatomical template was segmented into gray and white matter using the SPM tissue probability map of an adult brain. In the normalization step the resulting co-registration and segmentation parameters were then transferred to the slice-time corrected functional images. Finally, these were then smoothed with a Gaussian kernel of 8 mm FWHM (full width half maximum).

3.5.2 fMRI Statistics

The first level analysis was performed using a GLM based mass-univariate approach. Block designed models were created by convoluting a canonical HRF with each subjects timeseries. The subject's motion parameters were entered as further regressors. To counteract low-frequency signal noise and signal drift, a high-pass filter of 230 s was set.
Statistical results are shown at $p < 0.001$ and corrected for multiple comparison using a cluster-extent threshold of $k \geq 31$ voxels. A spatial autocorrelation of the data was estimated. Then a Monte Carlo simulation was run with 10'000 iterations, using a type I error voxel activation probability of 01001, and an estimated FWHM as a Gaussian smoothing kernel to derive the cluster extent threshold yielding the desired correction of multiple comparison at a $p < 0.05$ level (McCaskey et al., 2017; Slotnick, 2019)
The SPM Anatomy Toolbox was used for the anatomically localization of the fMRI results which are reported in MNI (Montreal Neurological Institute and Hospital) coordinates.
Behavioral data were analyzed with Excel (Version 2008, Microsoft, US) and SPSS (Version 20)

4 Results

4.1 Behavioral Results from Children and Adults

In total 16 children were assessed with a computer-based version of the fMRI task by solving one run each. Three integrative children with physical and/or mental problems were later excluded, and the final analyses were performed with the remaining 13 children (6 females, age = 7.2 – 10.2 years, mean ± SD = 8.6 ± 0.94). Behavioral measures are summarized in **table 2**.
The primary school students seem to struggle a lot with the subtraction task. Many trials were missed. One must consider the low mean accuracy (ACC) in the arithmetic blocks is partially due to the more frequently missed trials which are counted as errors. The big distributions of their ACCs further point out how their abilities with subtraction strongly differ at the age of 7 – 10. The control tasks were solved faster [$t(12) = -8.813$, $p < .001$] and with higher ACC [$t(12) = 8.208$, $p < .001$] but as well with large individual differences. Besides, the mean RT was decreased during the stress conditions of both task types [subtraction: $t(12) = 2.197$, $p < .048$, control: $t(12) = 2.870$, $p < .014$]. Especially the subtraction problems were much accurately in the stress condition [$t(12) = -3.039$, $p < .010$]. Thus, the stressors seemed to increase their total solving success.

Behavioral measure children	Subtraction	Subtraction + Stress	Control	Control + Stress
mean RT [s]	4.07	3.68	2.68	2.35
SD [s]	0.48	0.76	0.51	0.51
mean ACC [%]	49.3	65.6	86.0	88.6
SD [%]	21.8	26.2	17.6	14.1

Table 2. Behavioral results from 13 children solving the computer version of the fMRI paradigm. Mean reaction time (RT) standard deviation (SD) compared for the four block types: subtraction, subtraction + stress, control, control + stress. Equivalent results for the mean accuracy (ACC) and the SD. Missed trials were excluded in the RT measure but were counted as faults in the ACC calculation.

Behavioral results from 10 adults (5 females, age = 24.3 – 47.2 years, mean ± SD = 29.6 ± 7.57) were obtained (**table 3**). All adults (except of one) completed two runs while being measured in the fMRI scanner. As expected, they had no difficulties solving both task types in the given time. Mean RTs were therefore much lower than the provided max. 6 s. No trial was missed over all runs off all the subjects combined. Furthermore, the mean ACCs were over 95% for all four conditions. This was expected as the paradigm was designed for children. The subtraction problems were solved slower than the control task [$t(9) = -4.118$, $p < .003$]. During the stress conditions, the mean RTs are slightly shortened for subtraction tasks [$t(9) = -3.611$, $p < .006$]. The mean ACC on the other hand seems not to be affected by stress.

Behavioral measure adults	Subtraction	Subtraction + Stress	Control	Control + Stress
mean RT [s]	1.52	1.35	1.24	1.18
SD [s]	0.19	0.20	0.16	0.14
mean ACC [%]	96.2	96.1	96.8	97.1
SD [%]	4.1	4.1	5.1	2.1

Table 3. Behavioral data from the fMRI measurement from 10 adults. Mean reaction time (RT) and standard deviation (SD) as well as mean accuracy (ACC) and SD compared for the four block types. There were no missed trials in all the trials.

4.2 fMRI Results

The following presented results of brain activity for the different contrasts reached all the threshold of $p > 0.001$ and cluster-extent correction for multiple comparison ($k \geq 31$ voxels). Analysis of the subtraction task condition revealed activation in occipital areas including left and right inferior occipital gyri (IOG), the left middle occipital gyrus (MOG) and the right calcarine gyrus (**table 4**, **figure 2**).

Region	Cluster Size	Peak *t*-value	Peak MNI coordinates		
			x	y	z
Subtraction					
L inferior occipital gyrus	1209	8.61	-28	-78	-6
		7.43	-34	-70	-10
		6.77	-20	-80	-6
R inferior occipital gyrus	304	6.34	42	-77	-12
		6.23	38	-76	-4
		5.00	46	-68	-14
L middle occipital gyrus	89	5.64	-34	-86	10
R calcarine gyrus	45	5.53	12	-88	4
L posterior medial frontal	131	5.49	-4	4	52
		4.97	8	8	48
L middle occipital gyrus	45	4.76	-24	-66	38
Control					
L inferior occipital gyrus	102	5.50	-36	-74	-12
R inferior occipital gyrus	41	4.75	42	-68	-16
		4.54	46	-76	-6
Subtraction – Control					
L calcarine gyrus	208	6.28	-12	-58	0
		4.76	-8	-70	10
L inferior frontal gyrus	192	5.36	-40	12	26
		5.32	-38	20	22
R and L cuneus	193	5.32	-8	-92	16
		4.49	-6	-74	26
		4.46	4	-78	24

Table 4. Brain areas that showed significant activation during the subtraction and control tasks (both no stress conditions) in adults. Further, the contrast of arithmetic and control task related activation. ($p < 0.001$, $k \geq 31$, cluster-extent corrected)

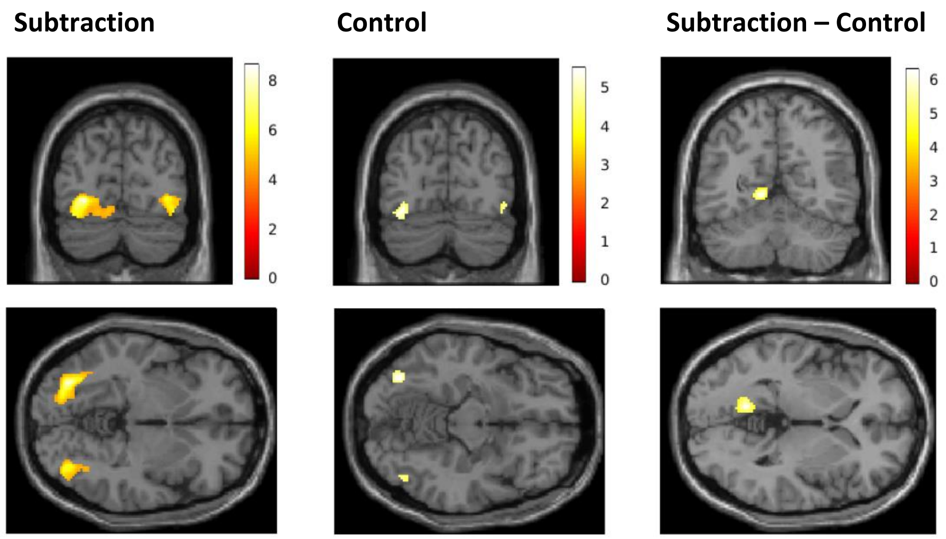

Figure 2. Task related activation shown on an adult template for the two task types: Subtraction and control (both without stress). Coronal and horizontal sections at the global activity maximum. Rather similar regions seem to be involved in both tasks. Thirdly, their contrasted activation ($p < 0.001$, $k \geq 31$, cluster-extent corrected).

Additionally, the left posterior medial frontal cortex (pMFC) showed significant activation. In the control task condition, the left and right IOG again reached significance but less pronounced than during the experimental task. The contrasting of their task related activation (asubtraction minus control) resulted in increased activity in the left calcarine gyrus, the left inferior frontal gyrus (IFG) and bilateral cuneus. The contrast and the total activity analysis of subtraction task could not show any significant activation in the IPS or other parietal areas related to numerical processing.

Region	**Cluster Size**	**Peak *t*-value**	**Peak MNI coordinates**		
			x	**y**	**z**
Subtraction: Stress – no Stress					
R superior temporal gyrus	478	7.94	62	-20	10
		7.57	64	-34	12
Control: Stress – no Stress					
R superior temporal gyrus	302	9.07	62	-12	10
		5.69	50	-20	8
L superior temporal gyrus	718	6.59	-38	-30	10
		6.51	-64	-42	16
		6.32	-60	-14	10
R superior temporal gyrus	51	5.00	66	-36	8
L middle occipital gyrus	46	4.94	-28	-94	-4
Subtraction + Control: Stress – No Stress					
R Rolandic operculum	1556	19.11	60	-16	12
(R superior temporal gyrus)		10.17	46	-30	10
		8.77	62	-32	12
L Rolandic operculum	1613	7.95	-34	-32	16
(L superior temporal gyrus)		7.87	-58	-12	6
		7.54	-46	-28	4
R inferior occipital gyrus	386	6.33	44	-78	-8
		5.64	36	-88	-4
R and L fusiform gyrus	441	5.47	34	-62	-16
		6.20	-28	-76	-12
		5.85	-26	-94	-4

Table 5. Brain areas that showed significant activation in the contrast of stress vs. no stress conditions for subtraction and control tasks in adults. In addition, the contrast of stress vs no stress on both tasks combined. ($p < 0.001$, $k \geq 31$, cluster-extent corrected)

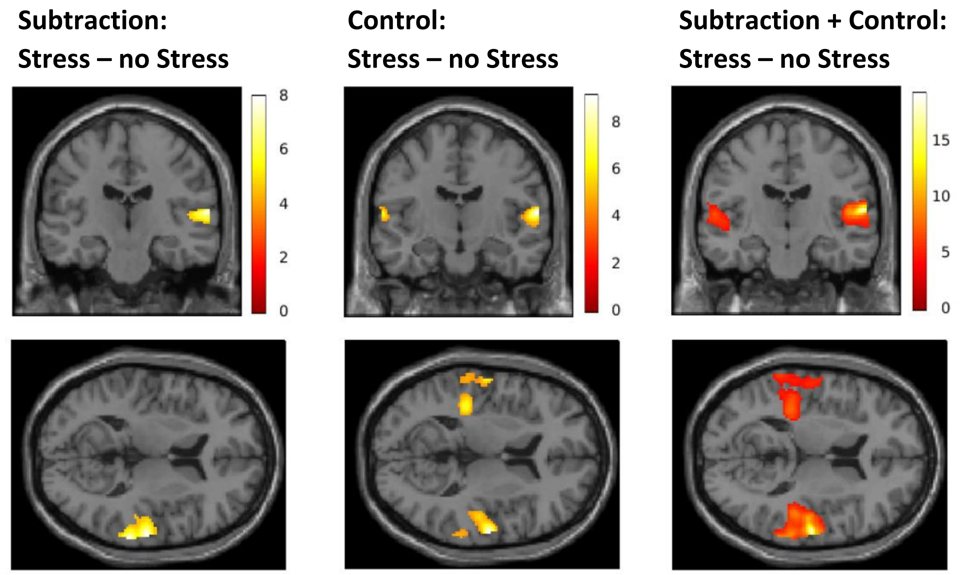

Figure 3. Contrast of stress related additional activation during subtraction and control tasks. Further, stress related activation for both task types combined ($p < 0.001$, $k \geq 31$, cluster-extent corrected).

The contrast of the subtraction task with and without stress (arithmetic: stress – no stress) showed increased activation of the right superior temporal gyrus (STG) (**table 5**, **figure 3**). The same area also reached the threshold in the contrasting of the control task during and without stressors (control: stress – no stress). The analysis of this contrast further found activity in the left STG and the left MOG to be significantly increased. Stress related activation for both task types combined (arithmetic + control: stress – no stress) demonstrated an increase in the Rolandic operculum bilaterally and further parts of the STG on both cerebral hemispheres. Furthermore, the right IOG as well as the right and left fusiform gyrus showed significant activation.
Other contrasts showed no significant activity. Thus, we found no threshold reaching signal for a specific control task activation (control – arithmetic), for a total math against control comparison [arithmetic (stress + no stress) – control (stress + no stress)], for a specific stress effect on math [arithmetic (stress – no stress) – control (stress – no stress)], and not for a specific stress effect on the control task [control (stress – no stress) – arithmetic (stress – no stress)].

5 Discussions and Conclusions

In the present study, we developed and tested a novel fMRI paradigm to investigate the interaction between mathematical performance and negative emotions. With this block-based factorial paradigm we behaviorally tested arithmetic problem solving (subtraction problems) and a novel control task during stress and non-stress conditions in 13 children and 10 adults. The brain activity of the adults was assessed by fMRI scanning in parallel.

The behavioral findings reveal that both task types (arithmetic and control) were not challenging for the adults resulting in high ACCs and low RTs. The lower mean RTs in the stress conditions could be caused by higher levels of alertness and a sense for the remaining time displayed by the shrinking time bar. Besides, the feedback might have motivated them to engage in the task more eagerly. The behavioral analyses of the primary school students showed that the subtraction task could often not be solved in the provided time. It was too difficult for most of the normal math achieving students. For future investigations, we aim to adjust the difficulty by using only single digits operands in the subtraction problems. Moreover, we could extend the answer time. However, one might lose the time pressure in the stress condition and further risk the block lengths to deviate even more. The control task seemed to be challenging for the students but of adequate difficulty with mean accuracy levels of 86% correctly solved trials. The stressors not only decreased the mean RT in children in both tasks but also increased the ACC in the subtraction task. Although, large individual differences in the ACCs of subtraction problems were observed, stress clearly improved the success in the subtraction task. This indicates a positive stress effect on math in normal achieving children. This finding should be reviewed in a larger children cohort and especially in children with math learning disabilities.

Functional activity analysis showed mainly occipital regions to be significantly activated during the subtraction task. We assume them to be important for the processing of the visual input during the task perception but also for basal numerical cognition (DeWind et al., 2019). The IOG has been associated with face recognition (Hadjikhani and Gelder, 2002). In its proximity a number form area (NFA) has been described to suggested to be specialized for numeral processing (Yeo et al., 2017). Therefore, it is possible that the observed activity reflects early number processing during subtraction solving. The significantly increased pMFC in the subtraction task most likely reflects the error monitoring behavior during subtraction solving (Danielmeier et al., 2011). The IFG has shown to be important for a huge variety of actions including language, working memory and empathy (Liakakis et al., 2011). Its activation in the contrast of arithmetic minus control condition could be related to higher working memory demands during the computation of subtractions. The increased activity in the cuneus might further be explained by higher levels of inhibitory control needed to press the correct answer buttons in the subtraction (Haldane et al., 2008). Our results show thereby more domain general features of visual task processing and executive function. More brain areas are significantly activated in arithmetic than in the control condition. This might be due to higher computational demands for subtractions than for square matching. However, the areas needed for the processing of subtraction tasks could just be more dispersed. The variety of subtraction types (single digit, double digits with and without crossing 10 boundary) require different solving techniques. Thus, they might be computed at distinct regions in the brain leading to more active brain regions. Against our hypotheses, functional activity analysis surprisingly found no significant activation in the IPS or other parietal regions in adults during in the contrast of arithmetic vs control tasks. We assume the square matching task to activate similar brain regions used for the subtraction problems. The activity was then cancelled out in the contrast.

The contrasting of the stress vs. no stress condition revealed for both arithmetic and control significant activation in the STG. The STG includes the Heschl’s gyrus (HG) and the primary auditory cortex (PAC) and is important for the encoding of speech sound (Yi et al., 2019). However, it has also been associated

with fear processing and is believed to connect to the amygdala (De Bellis et al., 2002). As we included the feedback in block-designed model, the activity is presumably related to the sound processing of the aural feedback. Nevertheless, increased STG signal might also indicate fear processing which could be induced by the stressors. To disentangle the role of the STG in the stress condition, the aural cue could be removed in further trials. The global stress effect on both task types combined involved the Rolandic operculum of both hemispheres. The Rolandic operculum, a region at the edge of the STG, was proposed to be important for gustation (Faurion et al., 1999), for speech production (Tonkonogy and Goodglass, 1981), and interoceptive awareness (Blefari et al., 2017). However, it has also been described to part of the cingulo-opercular network. An increased functioning of this network was associated with anxiety and anxiety disorders (Sylvester et al., 2012). The increased Rolandic operculum activity might be explained by elevated anxiety in the stress condition.
The detected activation fusiform gyrus and in the right IOG presumably reflects the processing of the smileys in our feedback by triggering the subject's innate face recognition (McCarthy et al., 1997). Although their activity should be cancelled in the contrast, it might be possible that due to solving speed differences more control tasks were solved on average and thus more feedback was displayed.

Summarized, the piloting of the fMRI paradigm provided insight into the solving behavioral of children and brain activity changes in adults during the two task types and the stress condition. The high error rate of primary school students in the subtraction task emphasizes the use of easier, single digit subtractions. Furthermore, the testing of more unified subtraction problems could potentially result in a more focal and thus stronger brain activation and thereby result in thresholding signal in math associated areas. Although the square matching task seemed to be of adequate difficulty, it was not effective as a control task. It activated too similar brain areas and thereby erased the desired math-specific signal in the contrast. For future studies the control task could be changed by removing the overlap in the squares and thus reducing the visuo-spatial demand.
Behavior analysis in children revealed a positive stress effect on subtraction solving with the used stressors. FMRI measures in adults further showed activated brain regions that could be assigned to the processing of the feedback. Furthermore, areas have been found to be associated with stress and anxiety. They might reflect the applied negative emotional effect in our stress condition. Testing this paradigm in individuals with DD could help to disentangle the interplay between negative emotional processing and math disabilities.

The number of participants is a big limitation in this study. For future investigations more adults as well as children should be accessed with an adjusted version of this paradigm. Furthermore, the test environment for children and adults deviated a lot as latter solved the task in the MR scanner. Through the implementation of all four block types in one run we lost signal detection power and might thereby have missed crucial activation. On the other hand, this allowed us to investigate in the effects of negative emotions on subtraction tasks in a more detailed view.

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